LAW OFFICES
KLEINFELD, KAPLAN AND BECKER
1140 NINETEENTH STREET, N.W.
WASHINGTON, D. C. 20036-6601
TELEPHONE (202) 223-5120
FACSIMILE (202) 223-5619
E-MAIL: kkb@kkblaw.com

ALAN H. KAPLAN
THOMAS O. HENTELEFF
RICHARD S. MOREY
PETER O. SAFIR
KINSEY S. REAGAN
PETER R. MATHERS
BONNIE A. BEAVERS
DANIEL R. DWYER
GLENN E. DAVIS
PRESCOTT M. LASSMAN
STACY L. EHRLICH
JENNIFER A. DAVIDSON
STACEY L. VALERIO

WEST COAST OFFICE:
ONE MARKET STREET
STEUART TOWER, SUITE 1450
SAN FRANCISCO, CA 94105-1313
TELEPHONE (415) 538-0014
FACSIMILE (415) 538-0016

VINCENT A. KLEINFELD
1907-1993

August 23, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

On behalf of Braintree Laboratories, Inc. ("Petitioner" or "Braintree"), the undersigned submit this petition under the Federal Food, Drug, and Cosmetic Act ("the Act") and Section 10.30 of the Food and Drug Administration ("FDA") regulations to request that the Commissioner of Food and Drugs ("the Commissioner"), based on serious safety concerns associated with the use of over-the-counter ("OTC") sodium phosphate bowel preparation products, reclassify such products as prescription only products and require a boxed warning on the labeling of such products calling attention to these serious safety concerns.

A. Actions Requested

The Commissioner is requested to issue a determination that drug products containing sodium phosphate and labeled for use as bowel preparations be: 1) subject to prescription limitations within the meaning of section 503(b) of the Act on the basis of sodium phosphate's documented toxicity and potentiality for harmful effects when used in bowel preparations and 2) regulated as "new drugs" within the meaning of section 201(p) of the Act on the basis that when used for bowel

00P-1472

CP1

preparation, sodium phosphate cannot be considered generally recognized as safe, whether marketed OTC or subject to prescription limitations. In addition, the Commissioner is requested to require a boxed warning on the labeling for all sodium phosphate bowel preparation products calling special attention to the serious safety concerns associated with the dose and contraindications of these products.

B. Statement of Grounds

1. Background

Oral sodium phosphate laxatives and bowel preparations are currently available in the United States as OTC preparations with professional use labeling. FDA first recommended monograph status for sodium phosphate in its March 21, 1975 advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic, and antiemetic drug productions. 40 Fed.Reg. 12902 (March 21, 1975). The agency's proposed regulation, in the form of a tentative final monograph ("TFM") for OTC laxative drug products, was published on January 15, 1985. 50 Fed.Reg. 2124 (Jan. 15, 1985). In addition to recommending Category I/Monograph status when used as an OTC laxative for the relief of occasional constipation, the proposal recommended Category I status when sodium phosphate is used as part of a bowel cleansing regimen in preparing a patient for surgery or for preparing the colon for x-ray or endoscopic examination. *See* proposed 21 C.F.R. § 334.80(a)(2), 50 Fed.Reg. at 2157.

On March 31, 1994, FDA proposed to amend the TFM for OTC laxative drug products to limit the OTC container size for sodium phosphate oral solution products and to add warnings to the labeling of such products. 59 Fed.Reg. 15139 (March 31, 1994). The agency found that taking more than 45 mL of sodium phosphate solution over a 10- to 12-hour period can result in significant

changes in electrolytes and may impose a risk of serious injury. Because of reported cases of accidental overdosing and resulting deaths, the agency proposed that 240 mL size containers of sodium phosphates oral solution no longer be available over-the-counter and the maximum OTC container size be limited to 90 mL. In addition, the agency proposed to include a warning statement informing consumers not to exceed the recommended dosage unless recommended by a doctor. On May 21, 1998, FDA finalized the package size limitation and warning requirements. 63 Fed.Reg. 27836 (May 21, 1998).

Also on May 21, 1998, FDA proposed to amend the OTC laxative TFM to include additional general and professional labeling for sodium phosphate drug products. 63 Fed.Reg. 27886 (May 21, 1998). FDA found that individuals with impaired renal function (including the elderly), heart disease, acute myocardial infarction, unstable angina, dehydration, or who are on diuretics are at risk for an electrolyte imbalance to occur with use of oral or rectal sodium phosphate products. "Sodium phosphates can cause alterations in serum levels of sodium, potassium, phosphate, chloride, and calcium and, in some people, such changes can be life threatening ... Hypocalcemia with subsequent low levels of ionized calcium may result in neuromuscular irritability, heart block, and cardiovascular failure." Id. at 27888. In addition, FDA found that "[f]atal or life-threatening consequences have resulted from excess dosages of sodium phosphates enemas in adults and in young children." Id. As a result of these dangers, the agency expanded substantially the warnings in the professional labeling and the OTC labeling for sodium phosphate drug products.[1]

---

[1]On December 7, 1998, FDA announced a stay of compliance until December 7, 1998 as to the warning and direction statements for OTC sodium phosphate drug products intended for rectal use only to permit sufficient time for relabeling these products. 63 Fed.Reg. 67399 (Dec. 7, 1998).

2. Because of the Serious Risks Associated with Their Use, Sodium Phosphate Bowel Preparation Products Should Be Deemed Unsafe for Use Except under the Supervision of a Practitioner Licensed by Law to Administer Prescription Drug Products

As FDA has concluded in the rulemakings relating to sodium phosphate products, there are serious risks associated with OTC use of sodium phosphate products, particularly when used as bowel preparations. As explained below, adequate directions for safe OTC use simply cannot be written. As a result of these risks, sodium phosphate products should only be used under the supervision of a practitioner licensed by law to administer prescription drugs. Contrary to the assertions of Fleet Co.[2] and InKine Pharmaceuticals[3] that oral sodium phosphate products used as bowel preparations are safe, several deaths and many injuries associated with the use of these products have been reported both in the literature and to FDA. Because there is evidence that increased use of large doses of sodium phosphate preparations may be expected,[4] a comprehensive review of the safety record of this product is imperative.

A simple internet and Medline literature search reveals four recent publications which detail five fatalities associated with use of oral sodium phosphate products as bowel preparations, in doses that were within or not far removed from current prescribing recommendations. In these cases, the doses were: 45 mL (30 g sodium phosphate) in two cases; 90 mL (60 g sodium phosphate) in one

---

[2]*See* Fleet submissions to Docket 78N-036L, attached as Exhibit A.

[3]*See* April 27, 2000 InKine letter to Docket 78N-036L, attached as Exhibit B.

[4]Vanner, SJ, MacDonald, PH, Paterson, WG, Prentice, RSA, DaCosta, LR, and Beck, IT. 1990. A randomized prospective trial comparing oral sodium phosphate with standard polyethylene glycol-based lavage solution (Golytely) in the preparation of patients for colonoscopy. The Amer. J. Gastro. 85:422-427.

case; and 120 mL (90 g sodium phosphate) in two cases. This highlights the narrow safety margin for sodium phosphate.[5] In each case, following bowel preparation with sodium phosphate, hyperphosphatemia was accompanied by hypocalcemia with tetany, hypokalemia and, ultimately, acute renal failure and death. In addition, the FDA database of reported adverse reactions reveals an additional four deaths and several reports of hypovolemia, hypocalcemia, hypokalemia and acute renal failure. Numerous other publications report hyperphosphatemia with symptomatic hypocalcemia resulting from the use of sodium phosphate products.[6] Indeed, these recent reports of death and injury have prompted both the Australian and New Zealand governments to reclassify oral sodium phosphate bowel preparations from OTC status to prescription only status.[7]

Some of these adverse events have been ascribed by the Fleet Co. to overdosage or use of the product in contraindicated patients, in spite of labeling with appropriate warnings.[8] Whether or not this is the case, these serious injuries continue to occur, which underscores the need for prescription only status. Indeed, based on available reports, once symptomatic hypocalcemia

---

[5]Ahmed, M, Raval, P, Buganza, G. 1996. Oral sodium phosphate catharsis and acute renal failure. The Amer. J. Gastro. 91: 1261-1262; Fass, R, Son Do, and Hixson, LJ. 1993. Fatal hyperphosphatemia following Fleet Phospho-soda in a patient with colonic ileus. The Amer. J. of Gastro. 88:929-932; Fine, A and Patterson, J. 1997. Severe hyperphosphatemia following phosphate administration for bowel preparation in patients with renal failure: two cases and a review of the literature. Amer. J. Kidney Dis. 29:103-105; Australian Adverse Drug Reactions Bulletin. Electrolyte disturbances with oral phosphate bowel preparations. Vol 16, No. 1 (Feb 1997).

[6]*See* bibliography attached as Exhibit C.

[7]Australian National Drugs and Poisons Schedule Committee (November 1997); New Zealand Medicines Classification Committee (November 1999).

[8]Post, SS. 1997. Hyperphosphatemic hypocalcemic coma caused by hypertonic sodium phosphate (Fleet) enema intoxication. J. Clin. Gastro. 24:192; Wood, TG. 1997. Oral Fleet Phospho-Soda: doses and interval between them. Dis. Colon Rectum 40:1396-1397.

develops, the mortality rate has been estimated to be as high as 33%.[9] Bowel preparation with oral sodium phosphate involves the ingestion of massive doses of sodium phosphate in order to induce a hyperosmotic diarrhea.[10] However, it is well known that the bowel avidly absorbs phosphate, resulting in a marked hyperphosphatemia and hypernatremia when phosphate is used for bowel preparation.[11] The phosphate and sodium overload are accompanied by numerous other biochemical changes.[12]

In clinical studies in which patients with renal failure, hypertension and other contraindications are carefully excluded, the biochemical changes are transient and without clinical sequelae,[13] although it has been noted that many studies do not perform or report patient serum chemistries.[14] Unfortunately, in clinical practice, patients are often not fully evaluated for

---

[9]Fine, A and Patterson, J., *supra* note 5.

[10]Gilman, AF, Goodman, LS, Rall, TW, and Murad, F. (eds). 1985. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 7th ed. Macmillan Publishing Co., NY.

[11]Id.; Lieberman, DA, Ghormley, J, and Flora, K. 1996. Effect of oral sodium phosphate colon preparation on serum electrolytes in patients with normal serum creatinine. Gastrointest. Endoscopy 43:467-469; Wiberg, JJ, Turner, GG, Nuttall, FQ. 1978. Effect of Phosphate or magnesium cathartics on serum calcium. Arch. Intern. Med. 138:114-116.

[12]Lieberman et al., *supra* note 11; DiPalma, JA, Buckley, SE, Warner, BA, Culpepper, RM. 1996. Biochemical effects of oral sodium phosphate. Dig. Dis. Sci. 41:749-753.

[13]Clarkston, WK, Tsen, TN, Dies, DF, Schratz, L, Vaswani, SK, and Bjerregaard, P. 1996. Oral sodium phosphate versus sulfate-free polyethylene glycol electrolyte lavage solution in outpatient preparation for colonoscopy: a prospective comparison. Gastrointest. Endoscopy 43:42-48; Huynh, T, Vanner, S, and Paterson, W. 1995. Safety profile of 5-h oral sodium phosphate regimen for colonoscopy cleansing: lack of clinically significant hypocalcemia or hypovolemia. The Amer. J. of Gastro. 90:104-107; Kastenberg, D, Choudhary, C, Weiss, E, Steinberg, S and the INKP-100 Study Group 1999. Sodium phosphate tablets (INKP-100) are safe and effective as a purgative for colonoscopy. Poster presented at the 1999 AGA; Vanner, et al., *supra* note 4.

[14]DiPalma et al., *supra* note 12.

contraindications. One researcher estimated from a survey of Canadian gastroenterologists that only 45% of physicians evaluated patients for renal failure prior to sodium phosphate bowel preparation.[15] The result is that underlying disease is frequently identified only posthumously or when a life-threatening event occurs.[16] Several reports have also indicated that bowel preparation with sodium phosphate products often result in colonic mucosal abnormalities which are endoscopically similar to Crohn's disease.[17] Such induced abnormalities can result in morbidity due to misdiagnosis and resultant therapy.

Many practitioners are comfortable with oral sodium phosphate bowel preparations. This is due in part to familiarity with these preparations as laxatives, their status as OTC with the attendant assumption of safety, the ease of administration of these products, and a pervasive advertising campaign promoting their use as bowel preparations. Use of sodium phosphate bowel

---

[15]Chan, A, Depew, W, Vanner, S. 1997. Use of oral sodium phosphate colonic lavage solution by canadian colonoscopists: pitfalls and complications. Can. J. Gastro. 11:334-338.

[16]*See, e.g.,* Ahmed et al., *supra* note 5; Boivin, MA and Kahn, SR. 1998. Symptomatic hypocalcemia from oral sodium phosphate: a report of two cases. The Amer. J. Gastro. 93:2577-2579; Campisi, P, Badhwar, V, Morin, S, and Trudel, JL. 1999. Postoperative hypocalcemic tetany caused by Fleet Phospho-Soda preparation in a patient taking alendronate sodium. Dis. Colon Rectum 42:1499-1501; Chan et al, *supra* note 15; Escalante, CP, Weiser, MA, and Finkel, K. 1997. Hyperphosphatemia associated with phosphorus-containing laxatives in a patient with chronic renal insufficiency. S. Med. J. 90:240-242; Fine and Patterson, *supra* note 5; Orias, M, Mahnensmith, RL, and Perazella, MA. Extreme hyperphosphatemia and acute renal failure after a phosphorus-containing bowel regimen. Am. J. Nephrol. 19:60-63; Vukasin, P, Weston, LA, and Beart, RW. 1997. Oral fleet phospho-Soda laxative induced hyperphosphatemia and hypocalcemic tetany in an adult. Dis. Colon Rectum 40:497-499.

[17]Chan et al., *supra* note 15; Driman, DK and Preiksaitis, HG. 1998. Colorectal inflammation and increased cell proliferation associated with oral sodium phosphate bowel preparation solution. Human Pathology 29:972-978; Zwas, FR, Cirillo, NW, El-Serag, HB, and Eisen, RN. 1996. Colonic mucosal abnormalities associated with oral sodium phosphate solution. Gastrointest. Endoscopy 43:463-466.

preparations, therefore, can be expected to increase. Because the patient population requiring bowel cleansing tends to be elderly, many of whom have undiagnosed age-related decline in renal function,[18] more serious adverse events can be anticipated. This is particularly problematic as many practitioners appear to be unaware of the appropriate dose and contraindications despite labeling to this effect.[19]

3. Because the Use of Sodium Phosphate as a Bowel Preparation May Lead to Death or Serious Injury, The Commissioner Should Require a Prominently Displayed Box Containing Information and Warnings Relating to the Serious Safety Hazards of Such Use

As described above, sodium phosphate bowel preparations have a highly questionable safety record. At a minimum, they should be regulated as prescription-only products with a thorough review and demonstration of safety and efficacy. In addition, due to a dangerous lack of awareness of the proper dose and contraindications for these products, labeling for sodium phosphate bowel preparations must include a box warning calling special attention to these areas, including the possibility of induced lesions. Since most clinical studies of oral sodium phosphate bowel preparations exclude patients with renal insufficiency or electrolyte disturbances, labeling should also include appropriate instructions for evaluations to be performed to rule out underlying renal and cardiac insufficiency and hypertension, particularly with respect to the elderly.

---

[18]Kirschbaum, B. 1997. The acidosis of exogenous phosphate intoxication. Arch. Intern. Med. 158:405-408.

[19]Chan et al., *supra* note 15.

We recommend the following black box warning be required on the labeling of all sodium phosphate bowel preparations:

> Do not exceed recommended dose. Before use, appropriate tests should be performed to rule out electrolyte, renal or cardiovascular abnormality. Serious and life-threatening adverse events have occurred with sodium phosphate in the presence of these conditions.

5. Conclusion

For the reasons set forth above, the Commissioner is requested to issue a determination that any drug products containing sodium phosphate and labeled for use as bowel preparations be: 1) subject to prescription limitations within the meaning of section 503(b) of the Act on the basis of sodium phosphate's documented toxicity and potentiality for harmful effects when used in bowel preparations and 2) regulated as a "new drug" within the meaning of section 201(p) of the Act on the basis that when used for bowel preparation sodium phosphate cannot be considered generally recognized as safe, whether marketed OTC or subject to prescription limitations. In addition, the Commissioner is requested to require a boxed warning on the labeling for sodium phosphate bowel preparation products calling special attention to the serious safety concerns associated with the dose and contraindications of these products.

C. Environmental Impact

According to 21 C.F.R. §25.25(a)(8), this petition qualifies for a categorical exclusion from the requirement for submission of an environmental assessment.

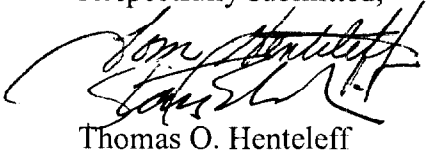
D. Economic Impact

According to 21 C.F.R. § 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of the petition.

E. Certification

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



Thomas O. Henteleff
Stacy L. Ehrlich
Counsel for Braintree Laboratories, Inc.